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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Graham P. Allaway, et al.

Serial No.: 09/412,284 Examiner: J. Parkin

Filed : October 5, 1999 Group Unit: 1648

For : METHODS FOR USING RESONANCE ENERGY TRANSFER-BASED ASSAY OF HIV-1 ENVELOPE GLYCOPROTEIN-MEDIATED MEMBRANE FUSION, AND KITS FOR PRACTICING SAME

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Commissioner for Patents
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SIR:

SUPPLEMENTAL DECLARATION
UNDER 37 C.F.R. §1.132 OF PAUL J. MADDON, M.D., Ph.D.

I, Paul J. Maddon, M.D., Ph.D., hereby declare that:

1. I am the same Paul J. Maddon who provided the earlier "Declaration Under 37 C.F.R. §1.132 of Paul J. Maddon, M.D., Ph.D.", executed March 7, 2002 ("prior declaration"), which I understand was appended as an exhibit to the Amendment filed March 8, 2002 by applicants' Counsel in support of the patentability of the claims of this application.

2. I understand the invention as presently claimed to be a monoclonal antibody which may be determined to be capable of specifically inhibiting the fusion of a macrophage-tropic primary isolate of HIV-1 to a CD4+ cell susceptible to infection by a macrophage-tropic

primary isolate of HIV-1, but not capable of inhibiting fusion of a T cell-tropic isolate of HIV-1 to such CD4+ cell, with the use of a method comprising:

a) contacting (i) a first appropriate CD4+ cell, which is labeled with a first dye, with (ii) a cell expressing the HIV-1 envelope glycoprotein of the macrophage-tropic primary isolate of HIV-1 on its surface, which is labeled with a second dye, in the presence of an excess of the antibody under conditions which would normally permit the fusion of the CD4+ cell to the cell expressing the HIV-1 envelope glycoprotein on its surface in the absence of the antibody, the first and second dyes being selected so as to allow resonance energy transfer between the dyes;

b) exposing the product of step (a) to conditions which would result in resonance energy transfer if fusion has occurred; and

c) determining whether there is a reduction of resonance energy transfer, when compared with the resonance energy transfer in the absence of the antibody;

d) contacting (i) a second appropriate CD4+ cell, which is labeled with a first dye, with (ii) a cell expressing the HIV-1 envelope glycoprotein of a T-cell tropic isolate of HIV-1 on its surface, which is labeled with a second dye, in the presence of an excess of the antibody under conditions which would normally permit the fusion of the CD4+ cell to the

cell expressing the HIV-1 envelope glycoprotein on its surface in the absence of the antibody, the first and second dyes being selected so as to allow resonance energy transfer between the dyes;

e) exposing the product of step (d) to conditions which would result in resonance energy transfer if fusion has occurred;

f) determining whether there is a reduction of resonance energy transfer, when compared with the resonance energy transfer in the absence of the antibody; and

g) comparing the determination made in step (c) with the determination made in step (f), wherein a decrease in transfer in step (c) but not in step (f) indicates that the antibody is capable of specifically inhibiting fusion of the macrophage-tropic primary isolate of HIV-1 to CD4+ cells, but not capable of specifically inhibiting the fusion of a T cell-tropic isolate of HIV-1 to the CD4+ cells,

wherein the monoclonal antibody is further capable under identical conditions of (a) specifically inhibiting 67% or greater of fusion of a CD4+ PM-1 cell to a HeLa cell expressing envelope glycoprotein from HIV-1_{JR-FL}, and (b) inhibiting 18% or less of fusion of a CD4+ SUP-T1 cell to a HeLa cell expressing envelope protein from HIV-1_{LAI}, wherein the antibody (i) does not cross-react with HIV-1 envelope glycoprotein or CD4, (ii) reacts with an antigen on

the surface of a PM-1 cell, and (iii) does not react with an antigen on the surface of a SUP-T1 cell.

I additionally understand that the invention is further directed to a method of inhibiting fusion of a macrophage-tropic primary isolate of HIV-1 with a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1, but not capable of inhibiting fusion of a T cell-tropic isolate of HIV-1 to such CD4+ cell, which comprises contacting the CD4+ cell with an amount of the above-described monoclonal antibody capable of specifically inhibiting such fusion so as to thereby inhibit such fusion.

Accordingly, the claimed invention relates to a monoclonal antibody having well-defined, specific physical characteristics, and uses thereof.

3. I have read and am familiar with the February 3, 2003 Office Action issued by the United States Patent and Trademark Office Examiner in connection with this application. I understand from the Office Action that the Examiner has maintained his rejection of the claims of the application and that in so doing he has commented concerning certain points set forth in my prior declaration filed in this case.

4. In my prior declaration, I stated (¶8) that the present specification teaches a straightforward, reproducible method for making and identifying an

antibody of the present invention. I further stated (¶9) that it is not necessary for one of ordinary skill in the art to know the antigenic determinants or epitopes on the surface of the whole cells used for immunization, or their structural configuration, in order to make an antibody having the characteristics of the antibody claimed in the present invention.

5. I understand that in response to my statements in the prior declaration, the Examiner asserted (see ¶7 on pps. 7-8 of the February 3, 2003 Office Action) that "since the disclosure fails to identify the immunogenic/antigenic determinants of interest and the structure of any given antibody, the skilled artisan has been extended an undue invitation to further experimentation". The Examiner further stated that "the claims are directed toward a specific chemical compound (e.g., antibody) with defined structural and binding characteristics. However the disclosure fails to provide any guidance pertaining to these structural and functional considerations". Further according to the Examiner, "the problem is that a reproducible method that produces antibodies with the specifically claimed characteristics was not provided".

6. Contrary to the Examiner's above-noted statements, it is irrelevant to both the amount and the level of experimentation needed to produce the claimed antibodies whether one skilled in the art has knowledge of the specific structure of the immunogenic

or antigenic determinants of an immunogen, or of the physical structure of the claimed monoclonal antibody. That is, the claimed monoclonal antibodies could be produced in the same manner whether or not one had knowledge of such structure of the determinants on the immunogen and/or structure of the antibody. In either event (i.e., with or without such knowledge), one could (i) immunize mice with the immunogen taught in the specification comprising the appropriate immunogenic/antigenic determinants, i.e., PM-1 cells; (ii) generate hybridomas upon such immunization, (iii) obtain antibodies by recovery of supernatant from such hybridomas; and (iv) subject such antibodies to the differential screening assay known as a resonance energy transfer ("RET") assay to identify antibodies having the claimed fusion-inhibiting characteristics. The above steps are carried out in the same manner whether or not the antigenic determinants and antibody structure are known. The essential teaching for obtaining monoclonal antibodies as claimed has been provided by the specification by identifying the proper immunogen having the appropriate antigenic determinants, i.e., PM-1 cells or equivalent cells, for eliciting the antibody along with the differential screening assays for selecting the monoclonal antibody meeting the physical criteria set forth in the claims. Thus, a lack of structural information on the antigenic determinants and monoclonal antibody would not necessitate any experimentation by one skilled in

the art beyond that required were such immunogenic or antigenic determinants known.

7. As demonstrated in ¶3 of my March 7, 2002 declaration, I am very familiar with the field of making monoclonal antibodies and am knowledgeable about the level of skill of those active in the field.

To my knowledge it is common for those in this field to characterize antibodies in terms of their physical characteristics such as function, without needing to characterize such antibodies in terms of their polypeptide structure or the structural identity of their immunogenic or antigenic determinants.

A representative example of such characterization is provided by U.S. Patent No. 4,381,295 to Kung et al. (the "295 patent"), a copy of which is attached hereto as **Exhibit A**. The '295 patent does not describe the antibody which is the subject of the invention in terms of either determinants or structure. Rather, as demonstrated by the '295 patent claims, the antibody is described in terms of its binding reactivity and the method by which the antibody is made.

8. The practice of describing an antibody by physical characteristics such as its function, rather than by polypeptide structure, extends as well to methods of using antibodies. Attached hereto as **Exhibit B** is a copy of U.S. Patent No. 5,993,816 to Lederman et al.

("the '816 patent"). The '816 patent contains claims to a method of inhibiting a humoral response by contacting T cells with an antibody. The antibody is not described in terms of its structure, but rather, it is characterized in the claims in terms of its binding characteristics.

9. Furthermore, with regard to the Examiner's statement in the Office Action that the disclosure fails to provide any guidance pertaining to the functional characteristics of the claimed antibody (see ¶5 herein), this application in fact provides considerable guidance regarding the functional characteristics of the claimed antibody. Specifically, this application describes the functional characteristics of at least four examples of the claimed antibodies, i.e., PA3, PA-5, PA-6 and PA-7. These functional characteristics are found, for example, in the data set forth in Table 3 on page 61 of the application, and the accompanying discussion of the same on page 60.

10. In light of the above facts, this application would readily enable one skilled in the field of making antibodies to make and use the antibodies as presently claimed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further

that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 4 August 2003

Paul J. Maddon

Paul J. Maddon, M.D., Ph.D.